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Three-component synthesis of 2-aryl-4-arylthio-tetrahydro-2*H*-pyrans via the Prins-cyclization

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ABSTRACT

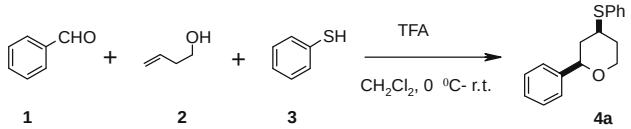
A three-component coupling of aldehyde, homoallylic alcohol and aryl thiol has been achieved in the presence of trifluoroacetic acid in dichloromethane at room temperature to produce 4-arylthiotetrahydropyrans in good yields with all cis-selectivity. This method is simple, selective and convenient for introducing a thiol group on a tetrahydropyran ring.

Multi- or three-component, one-pot reactions are highly important because of their wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery.[1] The Prins-cyclization is an important transformation to generate a wide variety of tetrahydropyrans, usually with net addition of an external nucleophile to the resulting carbocation.[2] Consequently, various nucleophiles such as halides, hydroxyls, organic nitriles, arenes, azide, and thiocyanate have been successfully utilized to terminate Prins-cyclization sequence.[2–4] Recently, 4-arylthiotetrahydropyrans are reported using electro-initiated cation chain reactions by means of intramolecular carbon–carbon bond formation between thioacetal and olefin.[5] Therefore, the introduction of a thiol functionality into an organic molecule continues to be a challenging endeavor in synthetic organic chemistry. Furthermore, there have been no reports on the direct one-pot preparation of 4-arylthiotetrahydropyrans via the Prins-cyclization and thiolation sequence in spite of thiocyanotetrahydropyrans being reported recently.[6]

In continuation of our research on the total synthesis of biologically active natural products involving Prins-cyclizations,[7] we, herein, report a versatile approach for the synthesis of 4-arylthiotetrahydropyrans via a three-component coupling (3CC) of aldehyde, homoallylic alcohol, and aryl thiol. The 3CC reaction was carried out in the presence of trifluoroacetic acid in dichloromethane. This approach provides a diverse range of 4-arylthiotetrahydropyrans in a single-step operation. Accordingly, we first attempted a three-component coupling of benzaldehyde (**1**), but-3-en-1-ol (**2**), and thiophenol (**3**) using 10 equiv of trifluoroacetic acid in dichloromethane. The reaction went to completion within 40 min in dichloromethane at room temperature and the desired product, 4-phenylthio-2-phenyl-tetrahydro-2*H*-pyran **4a** was isolated in 86% yield with all cis-selectivity (Scheme 1).

This result encouraged us to extend this process to various aldehydes and aryl thiols. Interestingly, aryl aldehydes such as *p*-chlorobenzaldehyde, *p*-methylbenzaldehyde, *p*-bromobenzaldehyde, 2-naphthaldehyde, and *p*-methoxybenzaldehyde underwent smooth coupling with but-3-en-1-ol to give the corresponding 2,4-disubstituted tetrahydropyrans in good yields (Table 1). Similarly, substituted thiols such as *p*-chlorothiophenol, *p*-methylthiophenol and 2-mercaptonaphthalene reacted readily with but-3-en-1-ol to produce 2,4-disubstituted tetrahydropyrans (entries c–g, i, and l, Table 1). Furthermore, 2-mercaptobenzothiazole also participated well in this reaction (entries h and j, Table 1, Scheme 2).

However, no reaction was observed in the absence of trifluoroacetic acid even after an extended reaction time (12 h). As solvent, dichloromethane gave the best results. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields and with high diastereoselectivity as determined from



Scheme 1.

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Table 1
TFA-promoted three-component synthesis of 4-thioaryltetrahydropyrans

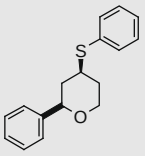
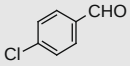
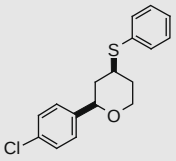
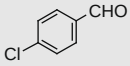
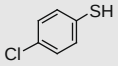
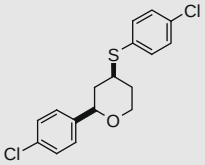
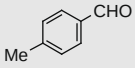
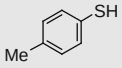
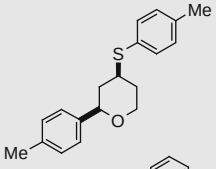
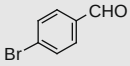
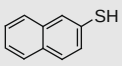
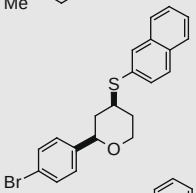
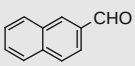
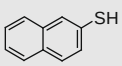
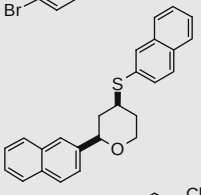
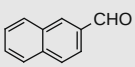
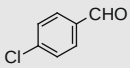
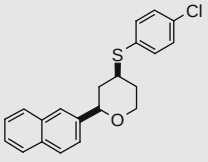
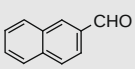
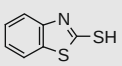
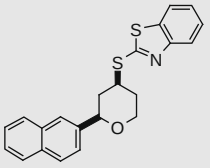
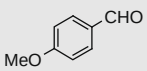
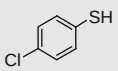
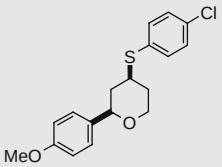
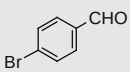
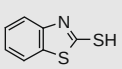
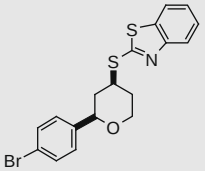
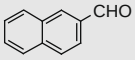
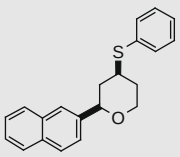
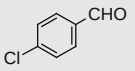
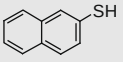
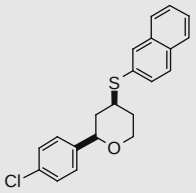
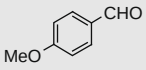
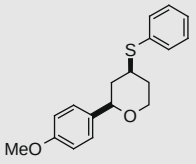
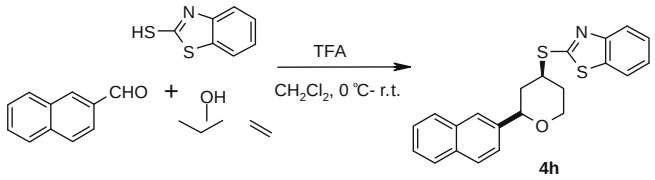
Entry	Homoallyl alcohol	Aldehyde	Thiol	Arylthiopyran[a]	Time (min)	Yield (%)[b]
a					40	86
b					35	89
c					45	90
d					30	87
e					45	82
f					50	85
g					45	83
h					70	81
i					30	85
j					70	78

Table 1 (*continued*)

Entry	Homoallyl alcohol	Aldehyde	Thiol	Arylthiopyran[a]	Time (min)	Yield (%)[b]
k					45	82
l					55	76
m					40	83

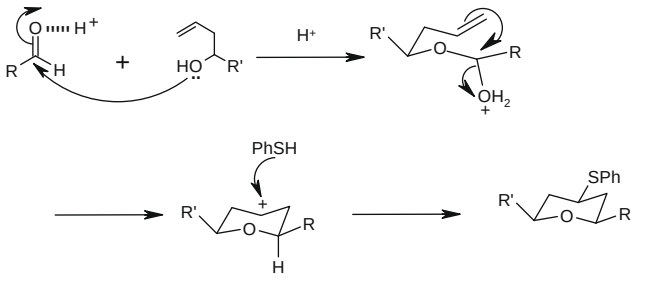
[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopies.
[b] Yield refers to pure products after chromatography.



Scheme 2.

the NMR spectra of the crude products. The cis-diastereomer was selectively produced as a racemic mixture for each reaction structure as confirmed by coupling constants (*J* values) and NOE experiments.[8] The formation of the products can be explained by hemi-acetal formation followed by Prins-cyclization and subsequent thiolation (Scheme 3).

A rationale for the all cis-selectivity involves formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the nucleophile.[9] Lewis acid catalysts including metal halides such as $InCl_3$, $InBr_3$, $BiCl_3$, and $ZrCl_4$ or metal triflates such as $Yb(OTf)_3$, $In(OTf)_3$, and $Sm(OTf)_3$ failed to give the desired product. Furthermore, solid acids such as Montmorillonte KSF clay, PMA, and TPA were also found to be ineffective. Surprisingly, no desired product was obtained using acetic acid. The use of $BF_3.OEt_2$



Scheme 3.

gave a mixture of thioacetal and 4-flourotetrahydropyran instead of 4-arylthiotetrahydropyrans. The scope of the trifluoroacetic acid catalyzed Prins-cyclization and thiolation sequence is illustrated with respect to various aldehydes and thiols and the results are presented in Table 1.[10] Aliphatic aldehyde/aliphatic thiol failed to give the desired product under similar conditions. Furthermore, we have examined the possibility of TFA functioning catalytically or at least in stoichiometric amounts. However, reduction in the concentration of TFA from 10 to 5 or 1 equiv produced cyclized products in diminished yields. This result indicates that the use of 10 equiv. TFA in dichloromethane is crucial to obtain the products in good yields.

In summary, we have developed a three-component, one-pot strategy for the synthesis of 4-arylthiotetrahydropyrans in a highly diastereoselective manner via a Prins-cyclization and thiolation sequence using trifluoroacetic acid as promoter. This novel approach provides a direct access to 2,4-disubstituted 4-arylthiotetrahydropyrans.

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10. *General procedure*: To a stirred solution of 4-chloro benzaldehyde (1.3 mmol), homoallyl alcohol (1 mmol) and 4-chlorothiophenol (2 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (10 mmol) slowly at 0 °C. The resulting mixture was allowed to warm to room temperature and the stirring was continued at 23 °C for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (2×15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 1:9) to afford pure 4-(4-chlorophenylthio)-2-(4-chlorophenyl)-tetrahydro-2*H* pyran. The products thus obtained were characterized by IR, NMR, and mass spectroscopies. Spectral data for selected compounds: **4c**: 4-(*p*-chlorophenylthio)-2-(*p*-chlorophenyl)-tetrahydro-2*H*-pyran: white solid, mp 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.40 (m, 8H), 4.07–4.34 (m, 2H), 3.45–3.65 (m, 1H), 3.15–3.35 (m, 1H), 2.02–2.11 (m, 1H), 1.85–1.96 (m, 1H), 1.59–1.75 (m, 1H), 1.42–1.59 (m, 1H). ^{13}CNMR (75 MHz, $CDCl_3$): δ 140.4, 134.52, 133.8, 133.3, 131.5, 129.1, 128.5, 127.1, 78.9, 67.9, 44.2, 40.8, 32.7. IR (KBr): ν 3423, 3077, 1475, 1484, 1392, 1347, 1247, 1201, 1122, 1089, 1038, 1006, 960, 822, 807, 766 cm^{-1}. LC–MS: 340[M+H]$^+$ **4d**: 4-(*p*-tolylthio)-tetrahydro-2-*p*-tolyl-2*H*-pyran: yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03–7.35 (m, 8H), 4.04–4.36 (m, 2H), 3.45–3.69 (m, 1H), 3.12–3.28 (m, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.02–2.12 (m, 1H), 1.82–1.90 (m, 1H), 1.48–1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 137.7, 137.4, 136.9, 133.5, 129.5, 128.9, 128.8, 125.6, 79.5, 67.8, 44.2, 40.8, 32.8, 20.8. IR (KBr): ν 3409, 3055, 2508, 1462, 1368, 1320, 1288, 1143, 1089, 816, 753 cm^{-1}. LC–MS: 298 M$^+$. **4j**: 2-(2-(*p*-bromophenyl)-tetrahydro-2*H*-pyran-4-ylthio)benzo[d] thiazole: white solid, mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.36–7.46 (m, 3H), 7.16–7.32 (m, 3H), 4.42–4.50 (m, 1H), 4.19–4.36 (m, 2H), 3.70–3.82 (m, 1H), 2.40–2.50 (m, 1H), 2.20–2.31 (m, 1H), 1.79–1.96 (m, 1H), 1.61–1.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 153.2, 140.7, 135.2, 131.4, 127.4, 126.0, 124.4, 121.6, 121.5, 120.9, 78.8, 67.9, 43.6, 40.5, 32.5. IR (KBr): ν 3426, 1488, 1450, 1442, 1423, 1259, 1232, 1125, 1081, 1000, 815, 760 cm^{-1}. LC–MS: 406 M$^+$.